2021 ESMO congress

Phase 1/2 study of Eprenetapopt (APR-246) in Combination with Pembrolizumab in Patients with Solid Tumor Malignancies

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DECLARATION OF INTERESTS

Haeseong Park, MD MPH

Research funding (institutional financial interest, local PI)

Ambrx, Aprea Therapeutics, Array BioPharma, BJ Bioscience, Bristol-Myers Squibb, Daiichi Pharmaceutical, Eli Lilly, Elicio Therapeutics, EMD Serono, Genentech, GlaxoSmithKline, Gossamer Bio, Hoffman-LaRoche, Hutchison MediPharma, ImmuneOncia Therapeutics, Incyte, Jounce Therapeutics, Mabspace Biosciences , MacroGenics, MERCK, Mirati, Novartis, Oncologie, PsiOxus Therapeutics, Puma Biotechnology, Regeneron Pharmaceuticals, Seattle Genetics, Synermore Biologics, TopAlliance Biosciences , Turning Point Therapeutics, Vedanta Biosciences, Xencor Inc.

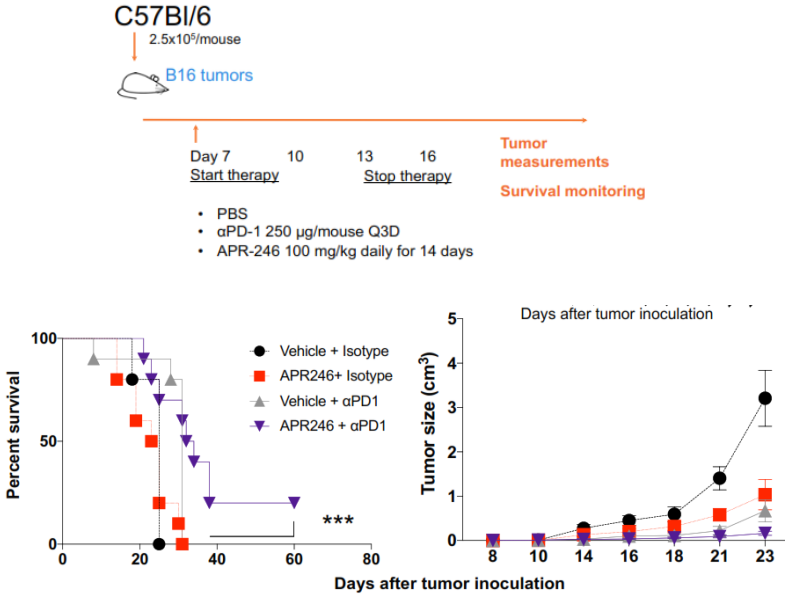
Background

Eprenetapopt (APR-246)

- First in class small molecule with novel mechanisms of action
- Induces apoptosis through stabilization of p53 structure
- Induces oxidative stress and ferroptosis
- Modulates tumor microenvironment and infiltrating immune cells
- Increases immune potentiating M1 polarized tumor-associated macrophages, and Granzyme B activity in CD8+ T cells*.
- Increases PD-L1 expression on macrophages, PD-1 expression on CD8+ T cells, and Foxp3+ Tregs in tumors.

Eprenetapopt + anti-PD1 therapy

- In *in vivo* studies, the combination of eprenetapopt with anti-PD1 antibody treatment led to a significant delay in tumor growth ($P < 0.001$) and improved survival of B16-bearing mice compared to anti-PD1 or eprenetapopt monotherapies ($P < 0.01$) and improved responses were also seen in MC38 colorectal cancer-bearing mice ($P < 0.01$).



*Ghosh et al., Cancer Res July 1 2019 79 (13 Supplement) 4843-4843

Phase 1/2 study of Eprenetapopt (APR-246) in Combination with Pembrolizumab in Patients with Solid Tumor Malignancies NCT04383938

Eprenetapopt 4500 mg/day Days 1-4 (every 21 days)

Pembrolizumab 200 mg D3 (every 21 days)

Phase1: Dose de-escalation

All solid tumors
Known TP53 mutation status
N = up to 18

Phase2: Expansion

Gastric/GEJ (anti-PD-1/L1 naïve) N = up to ~40	progressed or intolerant to first line treatment, IO naïve
Bladder/urothelial (anti-PD-1/L1 naïve) N = up to ~40	progressed or intolerant to first line treatment containing cisplatin-based chemotherapy, IO naïve.
NSCLC (prior anti-PD-1/L1 required) N = up to ~20	previously treated with anti-PD-1 or anti-PD-L1.

Primary Objectives

1. Safety and tolerability of eprenetapopt with pembrolizumab
2. MTD of eprenetapopt with pembrolizumab and RP2D
3. ORR (CR + PR) by RECIST 1.1

Data cutoff: 31 Jul 2021

Demographics (N=33)

As of July 31, 2021, there were 33 patients enrolled on study, 31 patients who initiated treatment, and 7 patients remained on study treatment. Treated patients included 6 in the safety, 3 in the gastric, 3 in the bladder/urothelial, and 19 in the NSCLC cohorts, respectively.

Patient Characteristics	Total Patients N=33
Median Age, yrs. (range)	65 (35-85)
ECOG PS (n) (%) 0 1 2	 3 (9 %) 28 (85%) 2 (6%)
Diagnosis (n) (%) NSCLC Gastric/GEJ Bladder/urothelial Other (Prostate & Colon)	 21 (64%) 6 (18%) 3 (9%) 3 (9%)
Median no. prior therapies (range) NSCLC Gastric/GEJ Bladder/urothelial Other (Prostate & Colon)	 5 (1-8) 4 (1-5) 1 (0-1) 8 (1-14)

Patient Characteristics	Total Patients N=33
TP53 Mutant Positive (n) (%)	25 (76%)
PD-L1 Expression Known (n) (%) -TPS -CPS - Other	 20 (61%) 14 (42%) 4 (12%) 2 (6%)
Prior IO Treatment in NSCLC, (n) (%) - Anti-PD-1 - Anti-PD-L1 - Anti-CTLA-4	 17 (81%) 11 (52%) 3 (14%)

Data cutoff: 31 Jul 2021

Safety Summary (N=31)

AE	All grade >10%	All grade related*
Dizziness	11 (36%)	10 (32%)
Nausea	10 (32%)	8 (26%)
Vomiting	10 (32%)	8 (26%)
Constipation	8 (26%)	1 (3%)
Decreased appetite	8 (26%)	4 (13%)
Fatigue	8 (26%)	5 (16%)
Dyspnoea	7 (23%)	2 (7%)
Anaemia	6 (19%)	3 (10%)
Abdominal pain	6 (19%)	1 (3%)
Headache	4 (13%)	4 (13%)
Tremor	4 (13%)	3 (10%)
Hyperglycaemia	4 (13%)	0
Hyponatraemia	4 (13%)	0
Muscular weakness	4 (13%)	3 (10%)

AE	Grade ≥ 3 in >1 patient
Anaemia	3 (10%)
Dyspnoea	3 (10%)
Dizziness	2 (7%)
Pain	2 (7%)
Malnutrition	2 (7%)

- No DLTs reported in safety cohort.
- Dizziness (2 pts/7%) was the only eprenetapopt related Grade ≥ 3 AE occurring in > 1 pt.
- 1 pt experienced a fatal AE (disease progression), which was assessed as not related to study treatment
- 1 pt with AEs fatigue, dyspnoea, maculo-papular rash leading to discontinuation of eprenetapopt

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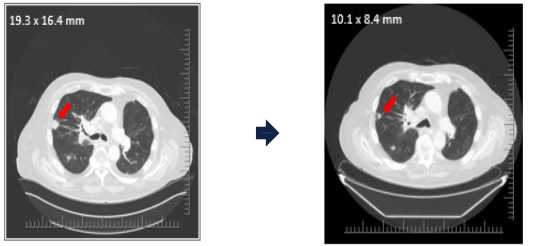
*Includes all AEs reported as related to eprenetapopt in > 2 patients.

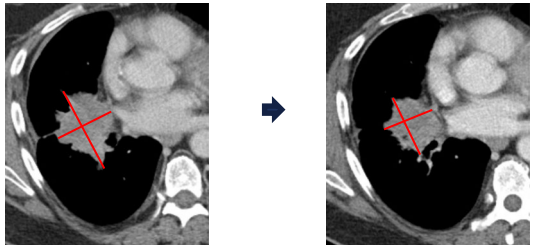
Data cutoff: 31 Jul 2021

Efficacy Summary and Target Lesion Reductions

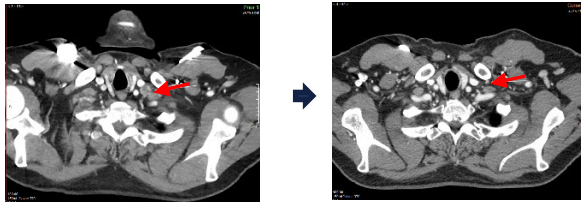
- 2/20 patients with NSCLC and prior IO therapy had reductions in tumor size
- 1/3 patients with IO-naïve bladder cancer achieved a CR



- 85 year old M with *TP53* mutant squamous NSCLC
- Prior treatment included carboplatin/paclitaxel/XRT and progression on atezolizumab
- 1st response assessment at 9 weeks showed reduction in target lesions of 26.7% from baseline. SD by RECIST, confirmed at 15 and 21 weeks, treatment ongoing.



- 55 year old M with *TP53* mutant squamous NSCLC
- Prior treatment included wedge resection of lobes, carbo + nab-paclitaxel X2, nab-paclitaxel, PD on nivolumab, and docetaxel and XRT
- 1st response assessment at 9 weeks showed reduction in total measurable disease of 8.2% from baseline. SD by RECIST, confirmed at 15 and 21 weeks, treatment ongoing.



- 75 yo M with locally advanced *TP53* mutant high-grade transitional cell bladder cancer
- Prior treatment for locally advanced disease included neoadjuvant platinum-based chemotherapy followed by radical cystectomy (ypT2, pN2, cM0).
- 3 months later had increased retroperitoneal, mediastinal, and left supraclavicular adenopathy.
- 1st response assessment at 9 weeks showed resolution of LAN. CR by RECIST.

Data cutoff: 31 Jul 2021

Conclusions

- Combination of eprenetapopt + pembrolizumab was safe and well-tolerated as evidenced by
  - Absence DLTs in the safety cohort
  - All grade AEs which were manageable with standard of care measures
  - 1 patient discontinued eprenetapopt due to AEs
- Preliminary efficacy signal of disease reduction in 2 of 20 patients with NCSLC previously treated with IO therapy and 1/3 patients with IO-naïve bladder/urothelial cancer who achieved CR
- Exploratory studies involving analyses of myeloid cells for inflammatory markers and immunosuppressive phenotype, and T cell phenotyping for exhaustion markers, are ongoing
- The trial continues to enroll and treat patients

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The Investigators and Sponsor would like to thank the patients for their participation in the study.

Active sites:

Massachusetts General Hospital
Dana Farber Cancer Institute
Vanderbilt University Medical Center
Mayo Rochester
Washington University
MD Anderson Cancer Center
University of Iowa
Mayo Arizona
Mayo Jacksonville

This trial is sponsored by Aprea Therapeutics.
For information regarding enrollment, please contact **info@aprea.com**

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